that the 17-carbon of the claimed compounds is always OH-substituted, that is, >C-R_g is >C(H)-OH for all claims. Further, Claim 1 is directed to steroid compounds that may be optionally substituted at the 1-, 3-, 4-, and 6-carbons.

Rejections of Claims 1-9 and 11-22 under 35 U.S.C. § 103(a)

A. Art Rejections

Sachdeva '598. Claims 1-9 and 11-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,054,598 to Sachdeva et al. ("Sachdeva '598"). It is the Examiner's position that the disclosure of **2-ethoxyestradiol** in Sachdeva '598 renders the present claims obvious.

D'Amato. Claims 1-9 and 11-22 are also rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,504,074 to D'Amato et al. ("D'Amato"). It is the Examiner's position that the disclosure of **2-methoxyestradiol** in D'Amato renders the present claims obvious.

The Examiner also cites the first two compounds of Table 2 and Table 1, lines 32, 37, 38 and 41 (column 8) against Claims 1-9 and 11-22. Applicants respectfully submit that the specific compounds of D'Amato's Table 1 to which the Examiner refers is not clear, and cannot be determined unambiguously from the information provided in the Office Action. However, it is Applicants' belief that the Examiner refers to the following species of Table 1: **2-methoxyestradiol, estradiol, estrone,** and **2-methoxyestradiol-3-*O*-methylether**. It is apparently the Examiner's position that the disclosure of these compounds in D'Amato renders the present claims obvious.

Pert. Further, Claims 1-9 and 11-22 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Pert et al. ("Pert"), DN 111:233338, abstract of Aust. J. Chem. **1989**, 42(3), 421-32. It is the Examiner's position that the disclosure of **4-bromo-2-methoxyestradiol** and the **2,4-dibromo-3-(2'-hydroxyl)ethoxy analog of estradiol** (compound I) renders the present claims obvious.

Ram. Claims 1-9 and 11-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,136,992 to Ram et al. ("Ram). It is the Examiner's position that Ram discloses **2-trifluoroethoxyestradiol**, which renders the present claims obvious.

Sachdeva '726. Claims 1-9 and 11-22 are also rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,051,726 to Sachdeva et al. ("Sachdeva '726"). It is the Examiner's position that the disclosure of **2-alkoxyestradiols** in Sachdeva '726, wherein the alkoxy group comprised a lower alkyl, renders the present claims obvious.

B. Examiner's Rationale

The Examiner acknowledges that the cited compounds do not have a substituent at the 16-carbon other than hydrogen. In contrast, all of the compounds of Claims 1-9 and 11-22 are substituted at the 16-carbon with other than hydrogen. *See* Claims 1 and 11 wherein R_{h1} and R_{h2} are independently defined, and requiring that both R_{h1} and R_{h2} are not H. Despite this structural difference, the Examiner considers the claimed compounds as mere "homologues" of the cited 2-alkoxy estradiols, characterizing the relationship between reference and claimed compounds as one "...of such close structural similarity that the disclosure of a compound renders prima facie obvious its homologue." *See* Office Action, page 4, 1st full paragraph.

The Examiner defines "[c]ompounds that differ only by the presence of an extra methyl group are homologues" (*see* Office Action, page 4, 1st full paragraph) which are obvious in view of each other. The Examiner further states that, "[t]he homologue is expected to be preparable by the same method and to have the same properties" and therefore "[t]his expectation is then deemed the motivation for preparing homologues." *See* Office Action, page 4, 3rd full paragraph.

Respectfully, Applicants traverse these rejections under 35 U.S.C. § 103(a) for the following reasons.

1. The Claimed Compounds are Not Homologues of the Reference Compounds

Citing *Ex parte Henze*, 83 USPQ 167 (POBA 1948) for support, the Examiner states that, "The skilled artisan would have been motivated to modify the teaching of the prior art to prepare homologs because it is recognized in the art that homologs are structurally similar and would be expected to possess similar properties." *See* Office Action, page 4, 2nd full paragraph. Applicants respectfully note that, in accordance with both *Ex parte Henze* and with MPEP 2144.09, the claimed compounds are *not* homologues of the reference compounds, therefore the reference compounds do not render Claims 1-9 and 11-22 *prima facie* obvious.

The Patent Office Board of Appeals in *Ex parte Henze* reversed the Examiner's rejection of the claimed compound 5-**methoxy**methyl-5-cyclohexyl hydantoin, in view of the reference compound 5-**phenoxy**methyl-5-cyclohexyl hydantoin, on the ground that it is not a homolog of the reference compound. The difference in these two species, namely **methyl vs. phenyl** substituted at the **same** position in the hydantoin molecule, was insufficient to render these compounds homologous. Further, MPEP 2144.09 defines homologs as "compounds

differing regularly by the addition of the same chemical group, e.g., by $-CH_2-$ groups." (Emphasis added.) Thus, by the MPEP definition, 2-methoxy estradiol and 2-ethoxy estradiol constitute homologues, but neither is homologous with any compound of Claims 1-9 and 11-22 for at least the reason that all the claimed compounds are substituted at the 16-carbon, whereas none of the reference compounds is substituted at the 16-carbon.

Respectfully, Applicants submit that the absence of a homologous relationship between the claimed compounds and those disclosed in Sachdeva '598, D'Amato, Pert, Ram, and Sachdeva '726 precludes these references from rendering Claims 1-9 and 11-22 *prima facie* obvious.

2. The Cited Art Does Not Recognize the Problem Nor the Source of the Problem

Respectfully, Applicants submit that a showing of *prima facie* obviousness has not been established by the Examiner because, among other reasons, the cited art does not teach or suggest the problem nor the source of the problem which Applicants have identified. *See In re Peehs*, 612 F.2d 1287, 204 USPQ 835 (CCPA 1980); *In re Zurcko* 111 F.3d 887, 42 USPQ2d 1476 (Fed. Cir. 1997).

Applicants recognize and identify the problems of 2-methoxyestradiol being metabolized to the much less active metabolite 2-methoxyestrone, *and* being deactivated by an additional metabolic deactivation pathway which results in the glucuronidation of 2-methoxyestradiol. *See* specification page 10, line 34-page 11, line 27. To solve this problem, Applicants' invention *adds steric bulk and/or modification of electrostatic characteristics at the 16-carbon* of 2-methoxyestradiol, to retard or prevent interaction of 17β-hydroxysteroid dehydrogenases and co-factor $NADP^+$ on this substrate. Further, the addition of steric bulk

and/or electrostatic modification at the 16-carbon may retard or prevent glucuronidation. It is believed that retardation or prevention of these two metabolic deactivation pathways prolongs the serum lifetime of 2-methoxyestradiol and other estrogenic compounds while retaining the desired anti-angiogenic and anti-tumor activity. *See* specification, page 11, lines 16-27. Indeed, initial screening of epimeric 16-ethyl-2-methoxyestradiol and related analogues showed that it is about equipotent to 2-methoxyestradiol in inhibition of HUVEC cell proliferation *in vitro*. *See* specification, page 17, lines 2-6.

Applicants respectfully submit that Sachdeva '598, D'Amato, Pert, Ram, and Sachdeva '726 fail to render Claims 1-9 and 11-22 obvious because none of these references recognizes the problem of multiple metabolic deactivation pathways, as in the Applicants' disclosure. The cited references disclose **merely** that some 2-alkoxy estradiols, none of which is 16-substituted, have antitumor activity.

To establish a *prima facie* case of obviousness where the advance lies in the discovery of the problem or the source of the problem, the Examiner would have to provide evidence that a person of ordinary skill in the art at the time of the invention would have expected a problem to exist. *In re Peehs*, 612 F.2d 1287, 204 USPQ 835 (CCPA 1980). The Examiner has provided no such evidence, and in fact has cited art which demonstrates the utility of the non-sterically hindered estradiol analogs the Applicants seek to avoid.

Applicants respectfully submit that the Examiner's assertion of obviousness can only be made with hindsight, using knowledge of Applicants' disclosure. Hindsight is impermissible and only facts gleaned from the cited references themselves may be used in making this determination (MPEP § 2142). As a result, knowledge of Applicants' disclosure must be put aside in making a determination of obviousness (MPEP § 2142).

Respectfully, Applicants maintain that Claims 1-13 and 21-25 are not rendered *prima facie* obvious by the cited references under 35 U.S.C. § 103(a) for these reasons stated herein, and respectfully request that this rejection be withdrawn and these claims be allowed.

3. The Cited Case Law Does Not Support the Finding of Obviousness

In addition to *Ex parte Henze* which Applicants discuss above, the Examiner has cited additional cases for the proposition that the close structural similarity of two compounds differing by only one or two methyl groups sufficed to find the one compound obvious in view of the other. *See* Office Action, page 5, 1st paragraph. The Examiner states that "homologs are obvious even in the absence of a specific teaching to methylate...." *See* Office Action, page 4, 3rd full paragraph.

Respectfully, Applicants submit that the cited case law does not support the finding of obviousness under 35 U.S.C. 103(a), and some cases the Examiner cited support the non-obviousness and patentability of Claims 1-9 and 11-22. Each of these cases is discussed below.

In re Wood, Whittaker, Stirling, and Ohta 199 USPQ 137 (CCPA 1978). The Examiner cited *In re Wood, Whittaker, Stirling, and Ohta* 199 USPQ 137 (CCPA 1978) for support of the § 103 obviousness rejection. The *In re Wood* court upheld the Examiner's rejection under 35 U.S.C. § 103 of a claim to more stable 7,7-dialkyl substituted compounds in view of less stable, unsubstituted compounds. However, it did so for lack of evidence of how the more stable claimed compounds might be expected to exhibit improved utility, specifically greater antimicrobial activity, over the unsubstituted reference compounds.

Respectfully, Applicants have provided evidence of how the claimed compounds would be expected to exhibit improved utility by identifying and addressing two metabolic deactivation pathways for unsubstituted 2-methoxyestradiol, which are diminished or prevented in the Applicants' invention. *See* specification page 10, line 34-page11, line 27. Applicants' design of steric and/or electrostatic manipulation of the 16-carbon in the claimed compounds, is expected to retard or prevent interaction of 17β-hydroxysteroid dehydrogenases and co-factor $NADP^+$. Applicants respectfully submit that the *In re Wood* holding does not render Claims 1-9 and 11-22 *prima facie* obvious.

In re Hoke 195 USPQ 148 (CCPA 1977). *In re Hoke* 195 USPQ 148 (CCPA 1977) was also cited by the Examiner for support of the § 103 obviousness rejection. The *In re Hoke* court upheld the Examiner's finding of *prima facie* obviousness to substitute a branched alkylene chain for an unbranched chain connecting the two active groups of a reference flocculant to form the Applicant's claimed flocculant. However the court's decision considered prior art raised by the Board that taught the Applicant's compounds both existed *and* exhibited desirable properties for use as flocculants (insensitivity to hydrolysis), which the Examiner had not considered.

Respectfully, the Examiner has provided no reference teaching that the Applicants' compounds of Claims 1-9 and 11-22 either existed or exhibited desirable properties (antiangiogenic properties) prior to Applicants' own disclosure. Applicants respectfully submit that the *In re Hoke* holding does not render Claims 1-9 and 11-22 *prima facie* obvious.

In re Lohr and Spurlin 137 USPQ 548 (CCPA 1963). Further, the Examiner also cited *In re Lohr and Spurlin* 137 USPQ 548 (CCPA 1963) for support of the § 103 obviousness rejection. The *In re Lohr* court upheld the Examiner's findings of *prima facie* obviousness of

claimed compounds containing two methyl groups at the 2- and 6-positions of a heterocyclic ring (a thioxane ring), whereas the reference compound does not contain dimethyl substitution on the heterocyclic ring. However, the *In re Lohr* Applicants developed a design premise based on one portion of the molecule in the reference patent, and then *disregarded their own design premise* by tenuously applying it to a different portion of the molecule, to support the non-obviousness of the claimed compounds. 137 USPQ at 550.

Respectfully, *Applicants have followed their design premise* based on identifying two metabolic deactivation pathways for unsubstituted 2-methoxyestradiol, by manipulating the steric and/or electrostatic features of the 16-carbon in the claimed compounds. Applicants respectfully submit that the *In re Lohr* holding is not applicable to their claimed compounds and does not render Claims 1-9 and 11-22 *prima facie* obvious.

In Re Magerlein 202 USPQ 473 (CCPA 1979). *In Re Magerlein* 202 USPQ 473 (CCPA 1979) was cited by the Examiner as another example in support of the 35 U.S.C. § 103 obviousness rejection. In overturning the rejection of the Applicants' claimed compounds under § 103, the *In Re Magerlein* court concluded that the "[a]ppellant has established that the dimethyl group at the C-16 position in his patented end products—the sole difference between his patented end products and those of [the reference]—is the feature that causes his patented end products to possess unexpectedly superior activity over the [reference] end products." 202 USPQ at 479. Respectfully, Applicants have shown the steric and/or electrostatic features of the 16-carbon in the claimed compounds to be important in slowing and/or preventing two metabolic deactivation pathways. Therefore, Applicants respectfully submit that *In Re Magerlein* **supports Applicants' assertion** that Claims 1-9 and 11-22 are non-obvious and hence patentable.

In Re Wiechert 152 USPQ 247 (CCPA 1967). *In Re Wiechert* 152 USPQ 247 (CCPA 1967) was cited for support of the § 103 obviousness rejection as well. The *In Re Wiechert* Examiner had rejected (and the Board upheld the rejection of) the Applicants' claimed **1-methyl** dihydrotestosterones as obvious in view of the reference **2-methyl** dihydrotestosterones, despite the fact that the claimed 1-methyl regioisomer was 7-times as potent as the reference compound. The Board cites the "positional" isomer (in fact, *regioisomer*) relationship between the claimed and reference compounds, and appears to uphold the Examiner's rejection on this ground. The *In Re Wiechert* court reversed the Examiner *and the Board*, finding these grounds insufficient, and holding the claimed compounds were non-obvious over their regioisomer. The court then remanded the case to allow the Applicant to respond to the Board's rejection.

Respectfully, Applicants submit that *In Re Wiechert* in fact supports the Applicants' assertion that Claims 1-9 and 11-22 are non-obvious. Unlike the compounds at issue in *In Re Wiechert*, Applicants' claimed compounds are not regioisomers of the reference compounds cited in Sachdeva '598, D'Amato, Pert, Ram, or Sachdeva '726, nor do they constitute *any* type of isomer of any reference compound, because they possess different molecular formulas, formula weights, and they are regio-substituted where reference compounds are not. Therefore, Applicants respectfully maintain that *In Re Wiechert* supports Applicants' assertion that Claims 1-9 and 11-22 are non-obvious and hence patentable.

Ex parte Henkel, et al. 130 USPQ 474 (POBA 1960). The Examiner also cited *Ex parte Henkel, et al.* 130 USPQ 474 (POBA 1960) in support of the § 103 obviousness rejection of Claims 1-9 and 11-22. The Examiner rejected the *Henkel* Applicants' claim to 1-phenyl-**3-methyl**-4-hydroxypyrazole as obvious in view of the prior art compounds 1-phenyl-4-

hydroxypyrazole (not 3-methyl substituted) and 1-phenyl-**5-methyl**-4-hydroxypyrazole. However, the Board did not uphold the Examiner's rejection on the basis of the similarity of the compounds, but rather on the ground the reference *specifically* disclosed examples of analogous compounds which indicate the possibility of the Applicants' 3-methyl substituted compounds.

Ex parte Henkel is distinguished from the Examiner's rejections in the present application, because there is no suggestion in the cited references to a possible 16-substituted analog of the reference compounds. Respectfully, Applicants submit that *Ex parte Henkel* does not support the Examiner's finding that Claims 1-9 and 11-22 are *prima facie* obvious.

Ex parte Fauque 121 USPQ 425 (POBA 1954). The Examiner cited *Ex parte Fauque* 121 USPQ 425 (POBA 1954) to support a finding of *prima facie* obviousness under § 103. The *Ex parte Fauque* Applicants' di(methylfuryl)methane was deemed obvious in view of the non-methylated di(furyl)methane reference compound, that is, the difference between the species is two methyl groups in each of two different rings. While the claimed compound was more stable that the reference compound, the Board upheld the Examiner's finding that such differences were obvious to a chemist from an inspection of the respective formulas, because such substitution patterns normally produce such differences.

Applicants respectfully maintain that *Ex parte Fauque* holding does not render Claims 1-9 and 11-22 *prima facie* obvious. Unlike the *Fauque* proceeding, the Examiner has provided no reference and no evidence that addition of steric bulk and/or modification of electrostatic characteristics at the 16-carbon of 2-methoxyestradiol, as Applicants have done, is expected to retard or prevent interaction of 17β-hydroxysteroid dehydrogenases and co-factor $NADP^+$ on this substrate, and retard or prevent glucuronidation. *See* specification, page 11, lines 16-27. Further, Applicants respectfully submit that none of the cited references render Claims 1-

9 and 11-22 obvious because none of these references recognizes the problem of multiple metabolic deactivation pathways, as in the Applicants' disclosure. The cited references disclose **merely** that some 2-alkoxy estradiols, none of which is 16-substituted, have antitumor activity.

To establish a *prima facie* case of obviousness where the advance lies in the discovery of the problem or the source of the problem, the Examiner must provide evidence that a person of ordinary skill in the art at the time of the invention would have expected a problem to exist. *In re Peehs*, 612 F.2d 1287, 204 USPQ 835 (CCPA 1980). The Examiner has provided no such evidence, and in fact has cited art which demonstrates the utility of the non-sterically hindered estradiol analogs the Applicants seek to avoid. Respectfully, Applicants maintain that *Ex parte Fauque* does not render Claims 1-9 and 11-22 *prima facie* obvious.

In Re Druey and Schmidt 138 USPQ 39 (CCPA 1963). Finally, *In Re Druey and Schmidt* 138 USPQ 39 (CCPA 1963) is cited by the Examiner as further support of the § 103 obviousness rejection. Respectfully, Applicants submit that the holding of *In Re Druey* regarding the standards for a showing of unexpected properties in the intermediate compound 3-amino-2-phenyl-pyrazole was overruled in *In Re Magerlein* 202 USPQ 473 (CCPA 1979), hence this case is not relevant to the Examiner's rejection of Claims 1-9 and 11-22.

As Applicants respectfully submit herein, *In Re Magerlein* in fact supports their assertion that Claims 1-9 and 11-22 are non-obvious and hence patentable.

Respectfully, Applicants maintain that the cited case law does not support the finding of obviousness under 35 U.S.C. 103(a) in view of Sachdeva '598, D'Amato, Pert, Ram, or Sachdeva '726. Each of the cited cases either is distinguished from the claimed invention, or supports the non-obviousness and patentability of the claimed invention. Therefore, for these

reasons stated herein, Applicants respectfully request that this rejection be withdrawn and these claims be allowed.

Conclusion

In view of the above remarks, Applicants respectfully maintain that Claims 1-9 and 11-22 are in condition for allowance. Such action is respectfully requested. If there are informalities remaining in the application which may be corrected by Examiner's Amendment, or there are any other issues which can be resolved by telephone interview, a telephone call to the undersigned attorney at 404.745.2420 is respectfully solicited.

Respectfully submitted,

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